MEDICINAL PLANTS AS SOURCES OF NEW THERAPEUTICS[1]

Walter H. Lewis[2] *and*
Memory P. Elvin-Lewis[2]

ABSTRACT

Indigenous peoples traditionally use a wide range of plants to maintain their health. Modern medicine has benefited substantially from anecdotal results of their empirical methodology by selecting needed candidates for a currently inadequate pharmacopeia to treat large numbers of illnesses. When the rapid destruction of diverse tropical forests, where the majority of cultured peoples using traditional medicine live, is related to the recent upsurge of interest in finding new antiviral, antineoplastic, and other agents, there is ample reason to justify learning what plants people use, how they use them, and under what circumstances the plants prove efficacious. These often ignored ethnobotanical findings set the stage for targeting plant materials that can be meaningfully analyzed for activity using appropriate biodirected assays and, when these are significant, for chemical isolation and characterization of active principles. Examples of ethnomedicinally selected western Amazonian plants used by Jívaro Amerindians having potential value by modern medical standards are described and evaluated.

There is great scope for new drug discoveries based on traditional medicinal plant use throughout the world (Cox et al., 1989; Farnsworth, 1984; Farnsworth & Soejarto, 1991; Moerman, 1991; Phillipson & Anderson, 1989; Schultes & Raffauf, 1990; Turner & Herbda, 1990; Tyler, 1986). In a recent review, Lewis (1992) outlined several hundred plants by medical category currently used in modern medicine and pharmacy, illustrating recent selections of natural products and their incorporation into modern pharmacopeias. He also showed how a culturally intact tribe, the Jívaro, use plants now, as they have for perhaps thousands of years, for health care on a daily basis. However, as he stated, "Serious dangers exist for the survival of such peoples and their cultures, and the ecosystems which nurture them and provide Western and traditional medicines with novel plant products for human well-being everywhere. In this race against ecosystem destruction, researchers in many disciplines must rally to provide the impetus to save global diversity while, at the same time, accelerating studies of ethnomedicine in consort with biomedical and chemical teams for developing new natural products and drugs needed by humans into the next century." As about three-quarters of the biologically active plant-derived compounds presently in use worldwide have been discovered through follow-up research to verify the authenticity of data from folk and ethnomedicinal uses (Farnsworth et al., 1985; Soejarto & Farnsworth, 1989), it is reasonable to conduct ethnobotanically directed research in order to optimize the search for novel pharmaceuticals.

This paper will examine five topics relating to ethnomedicinal targeting of plants as potential sources of new therapeutics: (1) initial collection of medicinal plants for screening, (2) evaluation of targeted collections, (3) plants as sources of drugs, (4) ethnomedicine of western Amazonian plants, and (5) intellectual property rights.

1. Collection of Medicinal Plants for Screening

There are a number of different ways to obtain plants for screening. These range from "random" or biodiversity-based selection to selections based on taxonomic, chemical, or ethnobotanical data, or any combination of these and other approaches. To date, most large plant collections are obtained "at random," with a goal of procuring as diverse a taxonomic representation as possible. The first National Cancer Institute (NCI) "random" procurement program (1960–1980) had several guidelines: a sample consisting of any plant part or combinations of plant parts would be acceptable if the sample could be supplied in an amount of 1

[1] We thank Gordon Cragg, Chief of the Natural Products Branch, National Cancer Institute, for testing crude plant extracts in the NCI's anti-HIV screen.

[2] Department of Biology, Washington University, St. Louis, Missouri 63130, U.S.A.

pound (0.37 kg) or more, while a duplication of species would be acceptable if samples were collected in different seasons or from different geographic areas. As stated by Spjut & Perdue (1976), "The orchids, for example, are not well represented because they are usually not sufficiently common." It is obvious that in such collections small or uncommon plants are selected against. In addition, certain plant parts would also not be widely collected even though commonly used in traditional medicine, such as root bark. Not only is root bark difficult to obtain, it is also destructive to vegetation. Collecting 0.37 kg of root bark, even in consort with other plant parts, might require many hours of work. Obviously, it cannot be justified to spend too much time for one collection when a deadline is approaching to collect 500 or more samples for NCI. What would be ignored? Root bark.

Spjut & Perdue also reported that, as collecting progressed, it became evident that certain families, notably the Apocynaceae, Celastraceae, Simaroubaceae, and Thymelaeaceae, were good sources of cytotoxic activity. As a result, a special effort was made to seek out plants of these families for screening. As they said, members of the Poaceae and a few other families proved poor sources of activity, hence further collecting of these plants was discontinued. Moreover, some suppliers of plants or extracts to the NCI program concentrated on medicinal plants. Clearly, this was not intended as "random" sampling, but rather "modified random." In this first NCI program, extracts representing 20,525 species (in 4716 genera and 317 families) were screened for antitumor activity, of which 2127 species, about 10.4%, in 1225 genera (26%) were found to be active (Spjut & Perdue, 1976).

What the NCI guidelines and recommendations introduced were taxonomic, chemical, and ethnobotanical factors into "random" collecting (Spjut, 1985). The Apocynaceae, which are diverse in secondary metabolites, were collected whenever the opportunity occurred, and correctly so, for the purpose of collecting was not to obtain a random sample, but to find plants active in antineoplastic screens. Therefore, the primary screening activity of 10.4% was based on a "modified random" collection. This frequency of activity probably was much higher than would be anticipated from randomness alone, and might more closely approximate the 6% activity found by Balick (1990).

Using various literature references, Spjut & Perdue (1976) divided species tested in the NCI assays into categories, based on traditional medicinal uses. Hence, for vermifuges, 29.3% of species (52.2% of genera) were active in antineoplastic screens, a figure about three times greater than in random screening results; for fish and arrow/dart poisons, 38.6% of species (65.8% of genera) and 52.2% of species (75% of genera), respectively, were 4 to 5 times more active in anticancer screens than in random screens; and, among four selected families having known traditional medicinal uses to treat cancer (Hartwell, 1967–1971), 19.9% of species (52.4% of genera) were active, about twice as numerous as would be expected from random screen results (Table 1). The Rubiaceae, however, proved to be more than three times as active as compared to random screens (Table 2). This categorization, while indirect, nevertheless shows that specific types of medicinal plants or selected families can provide valuable leads in increasing the frequencies of activity in certain primary assays. Since primary antineoplastic screens are based on detecting selective cytotoxicity for animal cells, it follows that those plants which are known to be highly toxic, like vermifuges and poisons, will tend to be more active in such screens than most me-

TABLE 1. Primary activity frequencies of plant species used in antineoplastic screens, NCI program 1 (from Spjut & Perdue, 1976).

	% active
20,525 spp. tested, 2127 spp. active	10.4%
Subset selected by traditional medicinal use:	
Vermifuges	29.3%
Fish poisons	38.6%
Arrow/dart poisons	52.2%
Four families known to treat cancer (Table 2)	19.9%

TABLE 2. Number of species in four selected families used against cancer in traditional medicine (Hartwell, 1967–1971) screened for antitumor activity, and number and percent of active species (modified from Spjut & Perdue, 1976).

	Number/percent of species			
Family	Traditional medicine	Screened	Active	% active
Fabaceae	180	136	25	18.4
Liliaceae	89	51	10	19.6
Rubiaceae	48	18	6	33.3
Rutaceae	22	21	4	19.0

dicinal plants, which are often used because of low toxicity.

We have shown that so-called "random" collecting of large numbers of plants is not at all random. However, individual collections may be randomized, and in these instances the collector, usually a systematist, may collect material for no special reason other than it is in flower or fruit, the typical collecting bias, or that it looks unusual (i.e., unknown to the systematist). If such collections turned out active, these finds would be serendipitous. But if a plant is collected because it is known to be used medicinally, even if for a different purpose than the intended screen, then this is not complete serendipity, for it may not have been brought to the laboratory if it were not for its traditional medicinal use. The initial discovery of the antineoplastic activity of *Catharanthus roseus* (L.) G. Don f. (Apocynaceae) was made through the good fortune that reviews of the pathology of treated mice indicated an induced leukopenic state, and that it was from this observation that the value of the species in treating leukemia was derived. Yet, Noble et al. (1958) and Svoboda (1961) included *C. roseus* in their antihypoglycemic screening programs because of its well-known folk use to treat diabetes. As such, this major discovery in medicine was based, in part, on initial targeting of traditional medicine.

The discovery in the early 1970s of the antineoplastic compound taxol from *Taxus brevifolia* Nuttall (Taxaceae) in a broad or random collection program of plants from the Pacific Northwest is presumably an example of pure serendipity. It is unlikely that the collector(s) knew that an allied species, *T. baccata* L., which is now known to possess frequencies of taxol even higher than *T. brevifolia* (Elias & Korzenevsky, 1992), had long been used in Asian Indian traditional medicine to treat cancer (Hartwell, 1971, see 1967–1971). In retrospect, based on this use in southern Asia, it would not be unusual to find an American species in the same genus having a similar compound and efficacy.

One of the best recent examples representing unqualified serendipity is the discovery of active anti-HIV compounds michellamines A and B in *Ancistrocladus korupensis* D. W. Thomas & Gereau (Ancistrocladaceae) (as *A. abbreviatus*, Gustafson et al., 1992) based on the original random collection made by Duncan Thomas in Cameroon. Thomas was accompanied by local helpers who had no name for this liana and who seemed even to be unaware of its existence in the ecosystem. Although the material was sterile, Thomas correctly surmised the identity of the genus, and as he had no prior ethnomedicinal or chemical data relating to it, and only passing taxonomic knowledge or interest, the collection and subsequent finding of anti-HIV activity in *A. korupensis* is an example of unqualified serendipity. In Malaysia, however, *A. tectorius* (Lour.) Merr. is used to treat dysentery (Perry, 1980). In generic terms, severe diarrheas, like dysentery, have a variety of etiologies which include bacteria, viruses, protozoans, and intestinal parasites, thus giving credence to the hypothesis that species of the same genus with anti-infective uses are likely to possess bioactive compounds.

As a consequence of the biases of major collecting programs, there are huge gaps in our screening profiles, which include many small plants, most infrequently occurring plants, and members of families judged low in secondary metabolites based on initial results involving often fewer than 5% of species and few assays. Certainly, some exciting finds will materialize from random collecting, which otherwise may not be found, but at what cost in time, energy, and funds compared to more focused collecting?

2. Screening of Targeted Collections

In their antiviral screening program, a Belgian group (Van den Berghe et al., 1985) reported that selection of candidates for screening when based on traditional medicinal data compared to several other methods "gave a five times higher percentage of active leads," even though in some cases the same active compounds were isolated from botanically unrelated active plants. In a preliminary test using plants submitted to the NCI anti-HIV screen, Balick (1990) found that random plant collections provided 6% activity, whereas those based on ethnobotanically selected "powerful plants" by an herbal healer yielded 25% activity, a four times greater frequency. Although these results were based on small numbers and were not statistically significant ($P = 0.10$), the trend was apparent, i.e., preselected medicinal plants had a greater frequency of anti-HIV activity than randomly sampled plants. These two examples, even though quantitatively limited, indicate that ethnobotanical selection may prove four to five times superior in detecting active agents during primary screening than by following the random method.

In September 1992, 50 crude aqueous and organic extracts, prepared following the NCI extraction protocol (G. Cragg, pers. comm.), from 25 vascular plants were submitted to the NCI's primary anti-HIV screening program. Collections rep-

TABLE 3. Ethnomedicinally targeted anti-infective plants tested in the NCI primary anti-HIV screen.

	Screens	Active (number/%)	Significance
NCI modified random	16,886	1429/8.5%	
Aqueous extraction	ca. 8443	1174/13.9%	
Solvent extraction	ca. 8443	225/3.0%	
Anti-infective targeted	50	15/30%	$P = <0.001$[1]
Aqueous extraction	25	10/40%	$P = <0.01$[2]
Solvent extraction	25	5/20%	$P = <0.05$[3]
Relative antiviral targeted subset	14	10/71.4%	$P = <0.001$[4]

[1] $\chi^2 = 20.9$, df 1; [2] $\chi^2 = 8.7$, df 1; [3] $\chi^2 = 4.9$, df 1; [4] $\chi^2 = 37.6$, df 1.

resenting 23 genera in 19 families from four continents had been prescreened by traditional medicinal use for anti-infective activity. About half of these collections represented a further selection of plants based on their use in the generic treatment of a viral infection considered to be ancestrally related to HIV and in some instances validated by traditional healers and specific antiviral primary screens. These results were compared with extracts of terrestrial plants obtained randomly (= modified random as already described) and tested by NCI in the same screens used from late 1987 through October 1992 (Cardellina et al., 1993, pers. comm.) during the second modified random screening program of NCI. Of the 50 samples tested, without regard to type of ethnomedicinally reported infection or source of information, 15 samples or 30% proved weakly to strongly active against HIV in vitro. When these results were compared with the 16,886 total extracts of terrestrial plants obtained randomly of which 1429 or 8.5% proved active in NCI's primary anti-HIV screens, our anti-infective prescreened samples proved highly significantly different ($P = <0.001$) (Table 3). Considering aqueous and organic extractions separately, significant differences were also obtained between preselected and random collections: 25 aqueous-extracted samples gave 10 active extracts against HIV (40%) compared to NCI's 13.9% activity ($P = <0.01$), and 25 organic-extracted samples produced 5 active extracts (20%) compared to NCI's 3% activity ($P = <0.05$). Selective prescreening based on ethnomedicinal use is, therefore, an effective means of obtaining targeted plant materials, at least when used as anti-infectives.

Anti-infective plants used in traditional medicine to treat a virus considered to be ancestrally related to HIV were included within the above data set (Elvin-Lewis, unpublished data). When examined using the primary anti-HIV assay, 10 of 14 samples or 71.4% (7 aqueous, 3 organic) proved active. Compared to random NCI collections, this subset of specifically targeted extracts was highly significantly different ($P = <0.001$). To our knowledge this specific example, as well as those representing the whole collection, provide the first statistically significant data confirming the value of ethnomedicinal preselection as a means of primary targeting terrestrial plants for further research (Table 3).

Samples of these active screens may be further tested by NCI to eliminate polyphenols and complex polysaccharides. Regardless of the outcome of these tests, however, and whether or not unique commercially useful compounds are present, use of plants by indigenous peoples as anti-infective aqueous ingestants in whole infusions or decoctions could prove efficacious, and therefore of immense value in traditional medicine for use throughout much of the tropical world. Moreover, lengthy and costly biodirected assays followed by chemical fractionations and characterizations often lead to disappointing results when toxicities prove too great. This is not often an outcome when plant remedies utilized as anti-infectives are ingested without apparent side effects and following procedures which may have been used for generations.

We have described anti-infectives as a whole and viral subset, but another way to group these collections and their assay results is to more clearly categorize the original ethnomedicinal sources of information as either primary or secondary. Primary sources we define as information obtained from those using plant materials and/or treating with them, based on personal experience with their preparation and administration, and judgment of efficacy. By secondary sources we include information obtained from literature, herbarium collection labels, and those persons having learned of plant uses, but who lack personal experience. The usefulness of this dichotomy in showing different

TABLE 4. Activities in anti-HIV screens of plant extracts used as anti-infectives based on primary and secondary ethnomedicinal data (activity = aqueous and/or solvent extracts).

Source	Plants	Active
Primary	7	7 (100%)
Secondary	18	4 (22.2%)

$P = <0.001$ ($\chi^2 = 12.4$, df 1).

values of primary and secondary ethnomedicinal data is illustrated by the anti-HIV activity of the 25 plant collections already described. We found that all seven primary source plants were active to some degree (weakly to strongly, either aqueous or solvent extracts or both), while only 22.2% of secondary source plants were active (Table 4). The difference between them is highly significant, indicating that the best ethnomedicinal information by far is that obtained from direct contact with those persons who are using plants to improve their health. This information then translates into highly focused and targeted data of enormous potential relevance in natural products research. As Balick (1990), Cox (1990), Farnsworth (1990), Lewis (1992), Malone (1983), and Plotkin (1988) argued, ethnobotany provides the mechanism for rapid assessments of the pharmaceutical potential of species, an obviously significant procedure when there is insufficient time and funds to test the majority of species.

3. PLANTS AS SOURCES OF DRUGS

Many plants are already sources or templates of numerous new pharmaceuticals. Just how numerous is often difficult to discern, for this number should include drugs used in a chemically unmodified form, as well as template molecules used to design and generate completely new drug substances (Kinghorn, 1992). At times the chemical histories of such modifications are difficult to trace from original plants to novel synthetic compounds, but a few examples will illustrate important, if often obscured, connections.

Atropine and scopolamine, tropane alkaloids that antagonize the action of acetylcholine, are isolated from a wide range of solanaceous genera, which are particularly common in Europe and the Middle East where they have had a long history of traditional medicinal use to relieve colic, to dilate pupils of the eye, and as poisons and ingredients of witches' brews. Today these compounds and their synthetics are widely used in antispasmodic preparations, to prevent motion sickness, and also to stimulate pupil dilation. Perhaps less well known is the field of synthetic atropine and cocaine analog chemistry, in which an amino alcohol used in the manufacture of the synthetic cocaine analog dimethocaine was incorporated into a synthetic analog of atropine, leading to the production of amprotropine (Sneader, 1985). Amprotropine became the forerunner of synthetic selective hormone antagonists, including the development of antihistamines, which are now immensely popular and are hailed by those who suffer from allergies as miracle drugs. This industry is worth billions of dollars annually.

Cromolyn, a synthetic derived from khellin, a chromone extracted from seeds of *Ammi visnaga* (L.) Lam. (Apiaceae), was introduced in the 1970s primarily as a preventative for bronchial asthma and other allergic conditions (Lewis & Elvin-Lewis, 1983). The plant had been used for centuries in traditional medicine of the eastern Mediterranean for, among other uses, treating bronchial congestion (Quimby, 1953), but it was first introduced to Britain for experimental research after WWII by a medical officer who had observed its use as an inhalant among the Bedouins. Sales of this molecule have exceeded $100 million annually for two decades, and they continue to rise.

Quinine, a quinoline alkaloid originally extracted from the bark of *Cinchona officinalis* L. (Rubiaceae) and perhaps other species, had a long history of use in montane Peru to treat intermittent fever or malaria. This knowledge was given by the Aguaruna Jívaro to the Jesuits in 1630, who then widely disseminated the bark containing quinine to Europe and elsewhere (M. C. Gnerre, pers. comm.). Many synthetic substitutes have been prepared, including quinacrine (mepacrine), found superior to quinine for the treatment and suppression of malaria and its analog chloroquine with fewer side effects, as well as reducing malarial fevers more quickly. Even so, malaria is still the most prevalent tropical disease in the world, with millions of cases reported annually to the World Health Organization. In addition, some strains of malarial parasites have become increasingly resistant to the 4-aminoquinoline synthetics, particularly chloroquine, so that resistance has spread to most of the major areas of the world where malaria is endemic and has now been detected in over 60 countries. Often, but not always, resistant strains can be controlled by the natural quinine product. What is needed are novel antimalarial nuclei with new modes of action: perhaps the sesquiterpene lactone artemisinin isolated from aboveground parts of *Artemisia annua* L.

(Asteraceae) is one answer. This plant has had a long history of use in Chinese traditional medicine to treat fevers (dating from Ge Hong, 340 A.D.), and when several thousand patients in southern China infected with *Plasmodium falciparum* or *P. vivax* used artemisinin, 91% or more were clinically cured (O'Neill et al., 1985; Lewis, 1992). This folk remedy may provide the important enrichment needed today to treat malaria and its forms resistant to the quinolines.

Tubocurarine, obtained particularly from *Chondrodendron tomentosum* Ruiz & Pavón and *Curarea toxicofera* (Wedd.) Barneby & Krukoff (Menispermaceae), blocks neuromuscular transmission and thus achieves reversible muscle relaxation. Learned from many Indian tribes in South America who used a decoction prepared from the roots and sometimes mixed with other plants as dart and arrow poisons, crude extracts of curare were traded by the Achuar Jívaro in the late 1930s to provide a ready supply during the experimental phase of drug development (Lewis et al., 1988). Commercial amounts were later obtained from Indian and Mestizo sources throughout Peru and Ecuador and also from other areas during 50 years of Western medical use. The alkaloid has only rarely been used since 1982, when atracurium was introduced as a short acting muscle relaxant utilizing the (bisbenzyltetrahydro) isoquinoline structure of tubocurarine, but incorporating a hydrolyzable ester portion within the molecule (Stenlake et al., 1983). In parts of Peru wild populations of these long-lived and slow growing lianas were threatened from overharvesting during a half century of commercial exploitation with no regard for managed sustainability. Since the collapse of this cottage industry in the 1980s, frequencies of these two species should slowly increase, and thus reverse what would have been endangerment or even extinction without the introduction of synthetic atracurium.

4. Ethnomedicine of Western Amazonian Plants

FIELD RESEARCH AND DATABASES

From 1982 to 1988, with students from Washington University and in collaboration with students and staff of the Museo de Historia Natural, Lima, we conducted ethnobotanical field research among four of the five Jívaro tribes (Achuar, Huambisa, Mayna, Shuar), the Candoshi, and the Mestizo populations of northern Peru and adjacent Ecuador. Ethnolinguists M. C. Gnerre and D. Fast W. were also an important component of our research for communication and for learning about the Jívaro cultures. These studies generated about 5500 collections of primary source information, largely based on a consensus of several local *curanderos* and others in each village who practice traditional medicine. Both men and women practitioners contributed data, the women often being more specialized and emphasizing pediatrics, obstetrics, and gynecology (Lewis & Elvin-Lewis, 1990; Lewis, 1992). No fewer than 125 angiosperm families involving hundreds of species have been recorded to treat a wide variety of illnesses (Lewis et al., 1987, 1988). On the other hand, *brujos* or witch doctors, who are male only and not represented in each community, and who practice largely with a few plants having hallucinogenic properties for contacting spirit worlds and for intercommunicating and telepathy, rarely are experienced using other plants for well-being.

In addition to a database covering all 5500 collections by family, genus, and species, with medicinal and other data, a second larger database has been developed for medicinal plants of South America as a whole. This compilation of about 14,500 entries of ethnomedicinal reports from the literature and unpublished herbarium specimen sources is based on our program at Washington University and the NAPRALERT database of the University of Illinois at Chicago. Included also are extensive files on phytochemical and biological activity of these South American plants obtained from current literature sources and organized with the ethnomedicinal data (Lewis, Elvin-Lewis, Farnsworth & Malone, in prep.). These anticipated volumes should be of value in selecting species used in traditional medicine for specific screens, especially when combined with our primary source data among one of the major tribal groups in the New World, which in total provides about 20,000 records of plants used medicinally in South America.

THERAPEUTIC POTENTIAL OF SPECIFIC PLANTS

With acculturation progressing rapidly among the Jívaro, much of the knowledge they possess may be lost before we are able to test even a fraction of what they use medically. This is important not only because such a loss would affect their long-term traditional health care, and thus make them even more dependent on Western medicine in the future, but it would prevent the introduction of potentially valuable medicinals into both Western medicine and traditional medical systems elsewhere. We shall examine a few examples from their pharmacopeia.

1. Wound healing Croton *(Euphorbiaceae)*. Early in our field research we observed the Jívaro taking sap from slashed stem trunks of *Croton lechleri* Muell.-Arg. (*uruchnumi*, cotton tree) and using it topically to treat cuts, abrasions, and other wounds or bites. We later learned that the sap, called *sangre de drago* (*grado*) in Spanish, obtained from this and other species of *Croton* was widely used in South America to heal various types of wounds. It was readily available from vendors on the streets of Lima and in markets throughout the region, to such an extent that this sap is undoubtedly the most commonly used traditional medicine in Peru. The tree is relatively common in both secondary and primary forests in the low eastern Andes and much of the upper Amazon basin, and as it need not be felled to obtain sap, overexploitation is not a concern in areas of Peru familiar to us.

We brought sap from Peru for testing, and our results have recently been published (Porras-Reyes et al., 1993). In brief, we found that the sap contains an active wound-healing aporphine alkaloid known as taspine. Healing properties were tested using different topical concentrations of taspine by the paired rat surgical incision model. Samples harvested at 5, 7, and 12 days post-wounding were examined for maximum breaking strength (MBS) and histology. Those treated with 250 μg of taspine, but not those with 50 μg or 10 μg of taspine, had significantly higher values for MBS than paired controls (26% by day 5 ($P = <0.005$) and 30% by day 7 ($P = <0.001$)). There was no difference between controls and taspine-treated rats at day 12. These values showed that healing occurred up to 30% more rapidly when using 250 μg of taspine compared to controls, low taspine concentrations, and 12 days post-wounding. Histological samples treated with 250 μg of taspine showed higher cellular infiltration and granulation, including fibroblast proliferation, at days 5 and 7. There was no difference between controls, those at day 12 post-wounding, or those treated with only 50 μg and 10 μg taspine.

We soon realized that the whole sap was an essential component of this useful alkaloid, for it provided the delivery system for topical application. Without it, the high insolubility of pure taspine presented a serious problem. Recently, we produced a semisynthetic of taspine with broad solubility and similar if not improved healing of wounds using our rat model. Chemical and biological studies are continuing.

2. Oxytocic Balansia *(Clavicipitaceae) parasitizing* Cyperus *(Cyperaceae)*. Jívaro women use *Cyperus articulatus* L. var. *nodosus* (H. & B. ex Willd.) Kuek. or *C. prolixus* HBK (*piripri*) tops to make crude infusions, which are drunk as oxytocic agents to aid in parturition or postpartum contractions and to reduce bleeding after childbirth. Sedge tops are essentially inert, but close examination of what the women use revealed a parasitic fungal sclerotia in apical sedge infructescences, which proved to be *Balansia cyperi* Edgerton (Lewis & Elvin-Lewis, 1990). This fungus is classified in the Clavicipitaceae, a family containing only one other genus, the well-known *Claviceps* or ergot of temperate regions. Jívaro women have, therefore, selected the only close relative of ergot found in their tropical ecosystem and used it for the same purposes as midwives did in European folk medicine centuries ago and as we do today in modern medicine. "Circumstantial evidence strongly suggests the presence of biodynamic principles similar to the ergot alkaloids in *B. cyperi*. Should this prove true, then the selection by Jívaro women of a plant parasite to aid in obstetrics is another sophisticated example of human ingenuity using empirical methodology" (Lewis & Elvin-Lewis, 1990). Within a year of this publication, Plowman et al. (1991) proved the existence of alkaloids in *B. cyperi* sclerotia similar to those of ergot alkaloids. There are numerous other examples, for these people, using plant medicines based on empirical selections, have found effective means of treating many of their illnesses.

3. Antimalarial plants. Root infusions of a number of species are drunk daily by Achuar Jívaro to treat malaria. To test efficacy, crude extracts were sent to the University of London School of Pharmacy to be evaluated for their ability to inhibit the incorporation of tritiated hypoxanthine into multidrug-resistant *Plasmodium falciparum* (K1 strain) (O'Neill et al., 1985; Phillipson & O'Neill, 1986). IC_{50} values ranging between 15 and 30 $\mu g/ml^{-1}$ were not highly active, but nevertheless worth pursuing, and further purification could lead to fractions with higher IC_{50} values (J. D. Phillipson, pers. comm.). Three of five species used as antimalarials by the Achuar showed weak to moderate anti-*Plasmodium* activity. A positive frequency of 60% with even modest activity against a *Plasmodium* multidrug-resistant strain is a striking example of Indian use of plants to treat widespread malaria in the upper Amazon basin, which may provide some protection against malaria for a population without recourse to quinine bark or antimalarial compounds.

4. Stimulating Ilex *(Aquifoliaceae)*. The last example of ethnomedicinal selection by the Jívaro

relates to the ritualistic use of *Ilex guayusa* (Lewis et al., 1991). Early every morning Achuar men drink up to 2 liters of a hot leaf decoction of this holly, and after about three-quarters of an hour each man vomits profusely. Vomiting is not due to emetic properties of the decoction, as might be suspected, but to a learned ritual associated with reducing the physiological effects of the liquid and also in providing recognition of passage from boyhood to manhood. We found the trimethylxanthine caffeine in all leaf samples, with concentrations ranging from 1.73 to 7.57% dry weight/weight, the maximum value representing the highest concentration of caffeine reported for any plant material. This tree and the one with 3.95% caffeine were avoided by the Achuar as "bad *wayus*," for even after emesis, when about half of the caffeine drunk is eliminated, these concentrations were still sufficiently great to leave the consumer high from too much caffeine. The person was nervous, irritable, and might even hallucinate, but after drinking *wayus* with lower caffeine concentrations, followed by emesis, the desired stimulating effects of caffeine use were obtained and a good day had begun. Boys, girls, and women were allowed to drink what was not used by the men, and boys became participants in the morning ritual once they had entered puberty. At some time in the past, the Jívaro were able to find this major stimulant in their ecosystem and to adapt its use culturally and physiologically in unique ways.

5. Intellectual Property Rights

As the majority of our plant collections include primary ethnomedicinal data targeted by contributors for specific medicinal uses, good faith requires that such information be recognized as intellectual property in a substantive way. We believe that access to such indigenous resources and the protection of intellectual property are complementary concerns. Therefore, an obligation exists to protect the interests of contributors, their villages or tribes if the knowledge is generalized, and the country of origin, so that should a product be produced and marketed or be used as an investigative tool in drug development or testing, then royalties, licensing fees, and other forms of compensation must be provided to these individuals, their communities or tribes as appropriate, and to the host country. If communication with local contributors or their tribes is difficult, e.g., the Achuar of Peru who have limited means of handling funds and use a language that is currently unwritten with very few non-Achuar understanding it, a trust fund must be established to be used for specific purposes to benefit individuals and the tribe. The host country will also be compensated through support of their scientific and cultural institutions. As Vice President Al Gore (1992) recently wrote, participating countries need investment of funds, while investing countries need to acquire genetic resources. These can be compatible endeavors.

Literature Cited

Balick, M. J. 1990. Ethnobotany and the identification of therapeutic agents from the rainforest. Pp. 22–39 *in* D. J. Chadwick & J. Marsh (editors), Bioactive Compounds from Plants. John Wiley & Sons, Chichester, U.K. and New York.

Cardellina II, J. H., M. H. G. Munro, R. W. Fuller, K. P. Manfredi, T. C. McKee, M. Tischler, H. R. Bokesch, K. R. Gustafson, J. A. Beutler & M. R. Boyd. 1993. A chemical screening strategy for the dereplication and prioritization of HIV-inhibitory aqueous natural products extracts. J. Nat. Prod. 56: 1123–1129.

Cox, P. A. 1990. Ethnopharmacology and the search for new drugs. Pp. 40–55 *in* D. J. Chadwick & J. Marsh (editors), Bioactive Compounds from Plants. John Wiley & Sons, Chichester, U.K. and New York.

———, A. R. Sperry, M. Tuominen & L. Bohlin. 1989. Pharmacological activity of the Samoan ethnopharmacopoeia. Econ. Bot. 43: 487–497.

Elias, T. S. & V. V. Korzenevsky. 1992. The presence of taxol and related compounds in *Taxus baccata* native to the Ukraine (Crimea), Georgia, and southern Russia. Aliso 13: 463–470.

Farnsworth, N. R. 1984. How can the well be dry when it is filled with water? Econ. Bot. 38: 4–13.

———. 1990. The role of ethnopharmacology in drug development. Pp. 2–21 *in* D. J. Chadwick & J. Marsh (editors), Bioactive Compounds from Plants. John Wiley & Sons, Chichester, U.K. and New York.

——— & D. D. Soejarto. 1991. Global importance of medicinal plants. Pp. 25–51 *in* O. Akerele, V. Heywood & H. Synge (editors), The Conservation of Medicinal Plants. Cambridge Univ. Press, Cambridge.

———, O. Akerele, A. S. Bingel, D. D. Soejarto & Z. Guo. 1985. Medicinal plants in therapy. Bull. WHO 63: 965–981.

Ge Hong. 340 A.D. Zhou Hou Bei Ji Fang [Handbook of Prescriptions for Emergency Treatment].

Gore, A., Jr. 1992. Essentials for economic progress: Protect biodiversity and intellectual property rights. J. N.I.H. Res. 4: 18–19.

Gustafson, K. R., J. H. Cardellina II, K. P. Manfredi, J. A. Beutler, J. B. McMahon & M. R. Boyd. 1992. AIDS-antiviral natural products research. Pp. 57–67 *in* C. K. Chu & H. G. Cutler (editors), Natural Products as Antiviral Agents. Plenum Press, New York.

Hartwell, J. L. 1967–1971. Plants used against cancer. A survey. Lloydia 30: 379–436, 1967; 31: 71–170, 1968; 32: 79–107, 153–205, 247–296, 1969; 33: 97–194, 288–392, 1970; 34: 103–160, 204–255, 310–360, 386–425, 1971.

Kinghorn, A. D. 1992. Plants as sources of medicinally and pharmaceutically important compounds. Pp. 75–95 *in* H. N. Nigg & D. Seigler (editors), Phyto-

chemical Resources for Medicine and Agriculture. Plenum Press, New York.

LEWIS, W. H. 1992. Plants used medicinally by indigenous peoples. Pp. 33–74 *in* H. N. Nigg & D. Seigler (editors), Phytochemical Resources for Medicine and Agriculture. Plenum Press, New York.

——— & M. P. F. ELVIN-LEWIS. 1983. Contributions of herbology to modern medicine and dentistry. Pp. 785–815 *in* R. F. Keeler & A. T. Tu (editors), Handbook of Natural Toxins, Volume 1: Plants and Fungal Toxins. Marcel Dekker, New York.

——— & ———. 1990. Obstetrical use of the parasitic fungus *Balansia cyperi* by Amazonian Jívaro women. Econ. Bot. 44: 131–133.

———, ——— & M. C. GNERRE. 1987. Introduction to ethnobotanical pharmacopeia of the Amazonian Jívaro of Peru. Pp. 96–103 *in* A. J. M. Leeuwenberg (compiler), Medicinal and Poisonous Plants of the Tropics. Pudoc Wageningen, The Netherlands.

———, ———, ——— & D. FAST W. 1988. Role of systematics when studying medical ethnobotany of the tropical Peruvian Jívaro. Pp. 189–196 *in* I. Hedberg (editor), Systematic Botany—A Key Science for Tropical Research and Documentation. Symb. Bot. Upsal. 28(3).

———, E. J. KENNELLY, G. N. BASS, H. J. WEDNER, M. P. ELVIN-LEWIS & D. FAST W. 1991. Ritualistic use of the holly *Ilex guayusa* by Amazonian Jívaro Indians. J. Ethnopharmacol. 33: 25–30.

MALONE, M. H. 1983. The pharmacological evaluation of natural products—General and specific approaches to screening ethnopharmaceuticals. J. Ethnopharmacol. 8: 127–147.

MOERMAN, D. E. 1991. The medicinal flora of native North America: An analysis. J. Ethnopharmacol. 32: 1–42.

NOBLE, R. L., C. T. BEER & J. H. CUTTS. 1958. Role of chance observations in chemotherapy: *Vinca rosea*. Ann. New York Acad. Sci. 76: 882–894.

O'NEILL, M. J., D. H. BRAY, P. BOARDMAN, J. D. PHILLIPSON & D. C. WARHURST. 1985. Plants as sources of antimalarial drugs. Part I. In vitro test method for the evaluation of crude extracts from plants. Planta Medica 1985: 357–472.

PERRY, L. M. 1980. Medicinal Plants of East and Southeast Asia: Attributed Properties and Uses. MIT Press, Cambridge, Massachusetts.

PHILLIPSON, J. D. & L. A. ANDERSON. 1989. Ethnopharmacology and western medicine. J. Ethnopharmacol. 25: 61–72.

——— & M. J. O'NEILL. 1986. Novel antimalarial drugs from plants? Parasitol. Today 2: 355–358.

PLOTKIN, M. J. 1988. Conservation, ethnobotany, and the search for new jungle medicines: Pharmacognosy comes of age . . . again. Pharmacotherapy 8: 257–262.

PLOWMAN, T. C., A. LEUCHTMANN, C. BLANEY & K. CLAY. 1990 (issued 1991). Significance of the fungus *Balansia cyperi* infecting medicinal species of *Cyperus* (Cyperaceae) from Amazonia. Econ. Bot. 44: 452–462.

PORRAS-REYES, B. H., W. H. LEWIS, J. ROMAN, L. SIMCHOWITZ & T. A. MUSTOE. 1993. Enhancement of wound healing by the alkaloid taspine defining mechanism of action. Proc. Soc. Exp. Biol. 203: 18–25.

QUIMBY, M. W. 1953. *Ammi visnaga* Lam.—A medicinal plant. Econ. Bot. 7: 89–92.

SCHULTES, R. E. & R. F. RAFFAUF. 1990. The Healing Forest: Medicinal and Toxic Plants of the Northwest Amazonia. Dioscorides Press, Portland.

SNEADER, W. 1985. Drug Discovery: The Evolution of Modern Medicines. John Wiley & Sons, Chichester, U.K. and New York.

SOEJARTO, D. D. & N. R. FARNSWORTH. 1989. Tropical rainforests: Potential sources of new drugs? Perspect. Biol. Med. 32: 244–256.

SPJUT, R. W. 1985. Limitations of a random screen: Search for new anticancer drugs in higher plants. Econ. Bot. 39: 266–288.

——— & R. E. PERDUE, JR. 1976. Plant folklore: A tool of predicting sources of antitumor activity? Cancer Treatm. Rep. 60: 979–985.

STENLAKE, J. B., R. D. WAIGH, J. URWIN, G. H. DEWAR & G. G. COKER. 1983. Atracurium: Conception and inception. British J. Anaesthesia 55: 3S–10S.

SVOBODA, G. H. 1961. Alkaloids of *Vinca rosea* (*Catharanthus roseus*). IX. Extraction and characterization of leurosidine and leuroctristine. Lloydia 24: 173–178.

TURNER, N. J. & R. J. HERBDA. 1990. Contemporary use of bark for medicine by two Salishan native elders of southeast Vancouver Island, Canada. J. Ethnopharmacol. 29: 59–72.

TYLER, V. E. 1986. Plant drugs in the twenty-first century. Econ. Bot. 40: 279–288.

VAN DEN BERGHE, D. A., A. J. VLIETINCK & L. VAN HOOF. 1985. Present status and prospects of plant products as antiviral agents. Pp. 47–99 *in* A. J. Vlietinch & R. A. Dommisse (editors), Advances in Medicinal Plant Research. Wissenschaftliche Verlagsgesellschaft, Stuttgart.